Consult from the Division of Metabolic and Endocrine Drug Products

Division Requesting Consult:	Division of Reproductive and Urologic Drug Products, HFD-580
Drug Name:	Lupron Depot 3.75 mg Lupron Depot-3 Month 11.25 mg
Duration:	12 Months
Sponsor:	TAP Pharmaceutical Products, Inc.
NDA #:	20-011/S-021 20-708/S-11
Consult Date:	16-August, 2001
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A. Consult Request

The Division of Reproductive and Urologic Drug Products (DRUDP) has requested an assessment of the level of risk associated with the adverse effects on the serum lipid profile seen in women when norethindrone acetate (NETA) 5 mg daily is added to Lupron for the treatment of endometriosis. The duration of treatment will be 6 to 12 months, or initial treatment will be for 6 months followed by retreatment for additional 6 month periods. The following questions are to be addressed:

1. Has the sponsor submitted sufficient data to permit a meaningful assessment of the effects of 6 and 12 months of treatment with 5 mg of NETA per day on lipids?
   A) Is the sample size adequate?
   B) Are the laboratory measurements appropriate and adequate?

2. What is the assessment of the risk(s) associated with the changes in lipids that were observed after 6 and 12 months of treatment with 5 mg of NETA per day?

3. Are these lipid-related risks likely to be significantly greater in women treated with Lupron plus NETA than those in women treated with Lupron alone?

4. If DRUDP were to extend the recommended treatment period with Lupron from 6 months to a maximum of 12 months for patients who also receive 5 mg NETA per day, what additional warnings or precautions would be included in labeling?

B. Background

Lupron Depot (LD) plus norethindrone acetate (NETA) "add-back" therapy is being evaluated by the DRUDP for the treatment of women with endometriosis. Lupron (leuprolide acetate), a gonadotropin-releasing hormone (GnRH) agonist, is currently approved for the treatment of pain associated with endometriosis. Treatment with Lupron or other GnRH agonists for longer than 6-months, or retreatment after the initial 6 months of therapy, is currently not recommended due to the hypoestrogenic effects of

treatment, particularly the loss of bone mineral density (BMD). Patient tolerance to treatment has also been limited, most commonly due to vasomotor symptoms. Investigators have attempted to decrease these side-effects and to allow treatment with GnRH agonists for longer than 6 months with the use of "add-back" therapies, which add-back sex-hormones to the GnRH agonist treatment[1]. Several small clinical trials have investigated the use of GnRH agonists with add-back therapies, usually either progestins alone or progestins plus estrogens, for up to one year. Add-back therapies, with progestins however, have been noted to have adverse effects, most notably unfavorable effects on the lipid profile.

NETA, a 19-nortestosterone derived progestin, is currently approved for the treatment of endometriosis, secondary amenorrhea, and abnormal uterine bleeding. NETA was selected for use as add-back therapy with Lupron based on previous research with norethindrone (NET). NET has been used with Lupron in doses of 0.35 to 3.5 mg per day (mean 2.04 per day), and NET has been used in combination with other GnRH agonists at doses of 1.4-10 mg per day. NET is not commercially available in the United States, and NETA was used instead as it has similar properties to NET. NETA is thought to be about ½ as potent as NET.

NETA and the other C-19-nortestosterone derived progestins possess androgenic activity, and have been associated with decreases in high density lipoprotein cholesterol (HDL-C), increases in low density lipoprotein cholesterol (LDL-C), and increases in the LDL/HDL ratio. The lipid effects appear to be dose-related. The adverse effects of NET on the lipid profile have been demonstrated in two small clinical studies that administered NET in combination with Lupron or nafarelin (another GnRH agonist). In one open-label, randomized, 48-week study by Surrey et al[2], 19 female patients with endometriosis were treated with LD plus sodium etidronate cycled with calcium carbonate and NET 2.5 mg daily (Group 1), or LD plus NET 10 mg daily (Group 2). Results showed that patients receiving both doses of NET experienced some decrease in HDL-C. Group 2 experienced larger decreases in HDL-C than Group 1, -37% vs -12% respectively, after 48 weeks of treatment. Persistent increases in LDL-C (+27 in Group 2, and +14% in Group 1) were also noted. Increases in the LDL/HDL ratio, and decreases in apo AI were also seen in Group 2. Both groups experienced some weight gain over the course of treatment, with Group 2 experiencing a significantly greater weight gain than Group 1 (7.7 ± 1.7 kg vs 3.4 ± 1.0 kg respectively). The primary differences between the two groups were in the greater lipid changes and weight gain associated with the higher doses of NET.

In another study by Riis et al[3], women with endometriosis were treated with nafarelin (n=9), or nafarelin plus NET 1.2 mg per day for 6 months (n = 17). Lipid results for the nafarelin plus NET group were notable for significant decreases in HDL-C of -10 to -15% during treatment, and for significant decreases in total cholesterol [TC] (-3 to –9%) and LDL-C (0 to –12%) during treatment and in the follow up period. Nafarelin alone significantly increased TC (+14 to +20%), and LDL-C (+5 to +20%) during treatment and follow up, and significantly decreased HDL-C (-9%) at 12 months in the follow up period.

Similar effects on the lipid profile have been demonstrated when NET and other progestins are used alone as contraceptive agents. In a study by Enk et al[4], depot injections of NET and depot-medroxyprogesterone (DMPA) [a 17-alpha-hydroxyprogesteone derivative] were administered for one year. NET showed persistent decreases in HDL-C of about –30% at 13 months of treatment compared to baseline. DMPA showed decreases in HDL-C and total cholesterol (TC) of about 10-20%. Another study by McEwan et al[5] evaluated the effects of long-term use (2-5 years, or >5 years) of depot-norethisterone enanthate (Nor-en) on serum lipids. Nor-en produced no differences from baseline in triglyceride (TG), TC, LDL-C and very low density lipoprotein cholesterol (VLDL-C). Decreases in HDL-C of -16% were seen in women who used Nor-en for 2-5 years, and decreases in HDL of -12% were seen in women who used Nor-en for >5 years. Similar decreases in HDL-C to those seen with NET and Nor-en have also been seen with other 19-nortestosterone derivatives administered orally (e.g. levonorgestrel)[6]. Effects on serum lipids for DMPA have been variable however, with some studies showing no effect on the lipid profile, and others showing mild increases in TC and LDL-C, and 10-20% decreases in HDL-C.

The effect on the lipid profile of GnRH agonists alone has also been studied[7,8]. The effect on the lipid profile has generally been mild, with either small increases in LDL-C and TC levels and little to no effect on HDL-C, or no effect on the lipid profile. These findings are consistent with the hypoestrogenic and hypoandrogenic effects of GnRH agonist treatment.

The effect of Danazol, another treatment for endometriosis, has also been studied. Danazol possesses strong androgenic activity and was compared to nafarelin in a study by Valimake et al[9] in patients with endometriosis (nafarelin n = 12, danazol n = 6). Both groups had decreases in TG and mild increases in TC. Danazol produced decreases in HDL-C and increases in LDL-C that recovered in the post treatment period. Nafarelin had no significant effects on HDL-C or LDL-C. These results suggest that the androgenic effects of treatment may be the predominant factor effecting serum lipids.

Although the effects of progestins on the serum lipids in women treated for endometriosis have been well documented in clinical trials, the long-term effects of these drugs on coronary heart disease (CHD) and cardiovascular (CV) morbidity and mortality have not been determined. Studies investigating the long-term effects of progesterone and estrogen administration on CV disease have been performed almost exclusively in users of oral contraceptive (OC) agents. The results of these studies have been conflicting, particularly as earlier studies investigated the effects of the older, higher-dose estrogen/progesterone combination OC agents that carried a higher risk of CV complications. More recent studies however, have found no increased risk of myocardial infarction (MI) in current users of low-dose OC agents[10], and other studies have shown an increased risk of MI only in OC users who are heavy smokers (>25 cigarettes per day)[11]. Results of the WHO Collaborative Study of Cardiovascular Disease and Steroid Contraception[12] found that OCs and heavy smoking together greatly increased the risk of MI, especially in combination with OCs containing 50 mcg of estrogen or more. These

results suggest a thrombotic rather than an atherogenic mechanism is involved in OC-related CV disease. The data from these studies however, did not allow for a firm conclusion about the possibility that progestin-containing OCs might affect the risk of MI in current users[13].

Past users of OCs have also been found to be at no greater risk of experiencing an MI than women who have never used OCs. A case-control study in women experiencing their first MI found that there was no increased risk of MI in former OC-users, whether use had ceased in the distant past or more recently[14]. These results suggest no prolonged effect on atherosclerotic CHD associated with OC agents in women; however it is not known if these findings would also apply to women treated with hormonal add-back therapy for endometriosis.

Despite the lack of clinical evidence that hormonal drug treatment with estrogen and progesterone can affect CV risk in pre-menopausal women, low HDL-C as a risk factor for CV disease has been firmly established by large epidemiologic trials[15]. Four large prospective epidemiologic studies have been performed in the United States that related levels of HDL-C and the incidence of CHD. These studies were: the Framingham Heart Study (FHS)[16], Lipid Research Clinics Prevalence Mortality Follow-up study (LRCF)[17], the Lipid Research Clinics Coronary Prevention Trial (CPPT)[18], and the Multiple Risk Factor Intervention Trial (MRFIT)[19]. These trials have evaluated older, predominantly male, higher-risk patients, and only FHS and LRCF included women. The FHS included men and women between the ages of 50 and 69, and LRCF included men and women ages 30-69. The results from these studies were generally consistent in demonstrating that a 1 mg/dL increment in HDL-C was associated with an increased risk of CHD and total CVD mortality of about 2%. The results in women in the LRCF were even more striking, with a 1 mg/dL increment in HDL-C associated with an approximately 4% decrease in CHD and total CV mortality. The relationship of HDL-C to all-cause mortality was weak however, and there were no differences in overall mortality observed between patients with different HDL-C levels. As these trials were performed in predominantly male, higher risk patients, it is not known if similar results would be obtained in a population of pre-menopausal female patients at low-risk of CHD, with secondarily induced (i.e., drug induced) low HDL-C.

Finally, the unfavorable effects on the lipid profile by progestin therapy must also be considered in the context of the patient's overall CV risk profile. The Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults presented updated clinical guidelines for cholesterol testing and management in May 2001[20]. The panel recommended that CV risk assessment and the intensity of risk-reduction therapy be adjusted to a person's absolute risk of CV disease. Risk determinants include the presence or absence of CHD, level of LDL-C and the major risk factors. The major risk factors are summarized in the following table:

Table 1: Major Risk Factors (Exclusive of LDL-C) That Modify LDL Goals*
Cigarette Smoking
Hypertension
Low HDL-C (<40 mg/dL)**
Family history of premature CHD (CHD in male first-degree relative, 55years; CHD in female first-degree relative <65 years)
Age (men ≥45 years; women ≥55 years)

*Diabetes is regarded as a CHD risk equivalent.
(HDL-C ≥60 mg/dL counts as a "negative" risk factor,; its presence removes 1 risk factor from the total count)

The panel identified LDL-C as the primary target of cholesterol-lowering therapy and recommended CHD risk status as a guide to the type and intensity of cholesterol-lowering therapy. HDL-C and TG are secondary targets for risk reduction, after the primary target of LDL-C. LDL-C treatment goals are based on risk status, and intervention with therapeutic lifestyle changes (TLC) and drug treatment are recommended as follows:

Table 2: NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories

Risk Category	LDL goal (mg/dL)	LDL Level at Which to Initiate TLC (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
With CHD or CHD risk equivalents (10-year risk >20%)	≤100	≥100	≥130 (100-129: drug optional)*
Without CHD and with ≥2 risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥160
Without CHD and with <2 risk factors**	<160	≥160	≥190 (160-189: LDL-lowering optional)

*Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
**Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

C. Studies Under Review

To support labeling changes to include treatment with Lupron for up to one year, or for retreatment after the initial 6 months of Lupron therapy, the sponsor has submitted 2 clinical studies in women with endometriosis who were treated with monthly Lupron plus add-back therapy. In one study, M92-878, women were treatment with Lupron alone, (Group 1), Lupron plus NETA 5 mg per day (Group 2), Lupron plus NETA plus conjugated equine estrogen (CEE) 0.625 mg per day (Group 3), or Lupron plus NETA plus CEE 1.25 mg per day (Group 4). In the other study, M97-777, all women were treated with Lupron plus NETA 5 mg per day for one year. As treatment with NETA was anticipated to cause adverse effects on the serum lipid profile, safety monitoring included evaluation of the effects of NETA on serum lipids.

1. Study M92-878

a) Study Design

Study M92-878 was a double-blind, randomized, parallel-group, multi-center study in 201 female patients with endometriosis accompanied by pain. Patients with cardiovascular disease or stroke were excluded from study participation. There were four treatment groups:
Group 1: Lupron Depot (LD) alone
Group 2: LD in combination with NETA 5 mg per day
Group 3: LD in combination with NETA and CEE 0.625 mg per day
Group 4: LD in combination with NETA and CEE 1.25 mg per day

All treatments were for a period of one year followed by a two-year post-treatment follow-up. All patients received LD 3.75 mg IM at four-week intervals for 52 weeks, and calcium supplements twice daily throughout the treatment and follow-up periods.

The primary efficacy outcome was improvement during treatment in pain. Suppression of estradiol (E2) and menses were used as efficacy markers. Safety was assessed by adverse events, and changes from baseline in vital signs, physical exam, BMD and laboratory tests. Serum lipid measurements for TC, LDL-C, HDL-C, and TG were obtained at baseline, at treatment Weeks 24 and 52, and during post-treatment follow-up.

Study visits and procedures are summarized in the following tables:

Table 3: M92-878 Study Visits and Procedures, Prestudy and Treatment Periods

Procedure	Prestudy		Treatment Period				
	Within 12 months of entry	Within 1 month of entry	Day 0	Weeks 4, 8, 12, 16, 20	Week 24	Weeks 28, 32, 36, 40, 44, 48	Week 52
Surgical Diagnosis Endometriosis	X						
Informed Consent		X					
Start Barrier Contraception		X					
Pregnancy Test		X*		X**			
Endometriosis/Fertility/ Menstrual History		X					
Medical History		X					
Endometrial Biopsy		X					
Clinical Evaluation Symptoms/Pelvic Exam		X	X	X	X	X	X
Pain Evaluation		X	X	X	X	X	X
Menstrual Record/ Daily Log		X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X
Blood Draw for E2			X	X	X	X	X
Bone Mineral Density		X			X		X
Physical Examination		X			X		X
Clinical Laboratory (including lipids)		X			X		X
Injection/Dispense Oral Medications			X	X	X	X	

*Within one week of entry
**Urine pregnancy test Week 4 only

Table 4: M92-878 Study Visits and Procedures, Post-Treatment Period

Procedure	Months Post-Treatment								
	Month 1	Month 2	Month 3	Month 4	Month 8	Month 12	Month 16	Month 20	Month 24
Clinical Evaluation Symptoms/Pelvic Exam	X	X	X	X	X	X			
Pain Evaluation	X	X	X	X	X	X			
Menstrual Record/ Daily Log	X	X	X	X	X	X			
Blood Draw for E2	X	X	X	X					
Calcium Supplementation	X	X	X	X	X	X	X	X	
Bone Mineral Density					X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Lipid Profile*					X	X	X	X	X

*Repeat until WNL or at baseline if baseline had been abnormal

b) Patient Disposition

Two-hundred and one (201) patients were randomized into the four treatment groups, and 120 patients (60%) completed one year of the study. Lipid results in the follow-up (post-treatment) period were available in only a small number of patients. Patient disposition is summarized in the following table:

Table 5: M92-878 Disposition of Patients

		Treatment			
	All	LD	LD/N	LD/N/CEE.625	LD/N/CEE1.25
Randomized, n (%)	201	51	55	47	48
Completed treatment, n(%)	120	32 (63)	31 (56)	33 (70)	24 (50)
Entered f/u Year 1, n(%)	62	39 (76)	39 (71)	35 (74)	26 (54)
Completed f/u Year 1, n(%)	50	14 (36)	10 (26)	14 (30)	12 (25)
Completed f/u Year 2, n(%)	16	4 (22)	6 (46)	5 (11)	4 (8)

c) Lipid Results

Total Cholesterol

Results of serum lipid analyses at Week 24 and Week 52 show a significant increase from baseline in TC for the LD-alone and LD/N/CEE1.25 groups. In both these groups, TC increased by about 10% from baseline, with similar results at Weeks 24 and 52. There were no significant changes in the LD/N and LD/N/CEE.625 groups. TC results by treatment group are summarized in the following table:

Table 6: M92-878 Total Cholesterol Results

Week	Treatment Group	n	Baseline	After Treatment	Mean % change from baseline	P-value*
24	LD-only	39	170.5	187.6	10	.001
	LD/N	41	179.3	174.8	-3	.722
	LD/N/CEE.625	42	172.2	180.0	5	.116
	LD/N/CEE1.25	38	170.4	187.6	10	.002
52	LD-only	23	168.0	187.7	12	.001
	LD/N	28	176.8	177.2	<1	.211
	LD/N/CEE.625	29	171.9	173.8	1	.632
	LD/N/CEE1.25	23	169.3	185.8	10	.004
Final	LD-only	40	171.0	186.9	9	<.001
	LD/N	41	179.3	177.8	-1	.231
	LD/N/CEE.625	42	172.2	177.9	3	.212
	LD/N/CEE1.25	39	170.7	190.2	11	<.001

*Within group change from baseline

HDL-C

Decreases in HDL-C from baseline at Weeks 24 and 52 were seen for the 3 NETA exposed groups, LD/N (-19% to –18% at Weeks 24 and 52 respectively), LD/N/CEE.625 (-25% to –28%), and LD/N/CEE1.25 (-11% to –16%). The HDL-C decreases did not change substantially between Week 24 and Week 52 for any group. There was no significant change in HDL-C for the LD-alone group. The HDL-C results are summarized in the following table:

Table 7: M92-878 HDL-C Results

Week	Treatment Group	n	Baseline	After Treatment	Mean % change from baseline	P-value*
24	LD-only	39	52.5	56.0	7	.024
	LD/N	41	51.8	41.9	-19	<.001
	LD/N/CEE.625	42	55.4	41.5	-25	<.001
	LD/N/CEE1.25	38	50.2	44.5	-11	<.001
52	LD-only	23	49.1	51.6	5	.798
	LD/N	28	51.2	42.1	-18	<.001
	LD/N/CEE.625	29	57.0	40.8	-28	<.001
	LD/N/CEE1.25	23	50.2	42.3	-16	<.001
Final	LD-only	40	52.4	55.3	6	.080
	LD/N	41	51.8	42.1	-19	<.001
	LD/N/CEE.625	42	55.4	41.8	-25	<.001
	LD/N/CEE1.25	39	50.0	45.4	-9	<.001

*Within group change from baseline

By NCEP guidelines (see Background) an HDL-C of <40 mg/dL is a risk factor for CHD. By these criteria, 75 patients (37%) had clinically relevant HDL-C decreases (HDL-C of <40 mg/dL) at any time during study drug treatment. Decreases in HDL-C to <40 mg/dL were more common in patients exposed to NETA (45-52% of patients) than in the LD-alone group (14%). HDL-C decreases to <40 mg/dL overall and by treatment group are summarized in the following table:

Table 8: M92-878 Patients with HDL-C Decreases to <40 mg/dL During Study Treatment

		Treatment			
	All	LD	LD/N	LD/N/CEE.625	LD/N/CEE1.25
Randomized patients, n (%)	201	51	55	47	48
Patients with HDL decreases, n (%)	75 (37)	7 (14)	23 (45)	20 (43)	25 (52)

HDL-C results in the post-treatment period were available in only a few patients per group, and appeared to return to baseline values in most patients (see Appendix).

LDL-C

LDL-C increased from baseline by +8 to +17% in all 4 treatment groups at Weeks 24 and 52, with similar results for all 4 groups at each time point. The LDL-C results are summarized in the following table:

Table 9: M92-878 LDL-C Results

Week	Treatment Group	n	Baseline	After Treatment	Mean % change from baseline	P-value*
24	LD-only	39	96.6	107.9	11	.034
	LD/N	41	101.5	113.2	12	<.001
	LD/N/CEE.625	41	98.1	114.4	17	<.001
	LD/N/CEE1.25	38	102.5	118.1	15	<.001
52	LD-only	23	95.5	110.1	15	.017
	LD/N	27	101.8	110.3	8	.009
	LD/N/CEE.625	29	96.4	112.0	16	.002
	LD/N/CEE1.25	23	100.9	116.1	15	<.001
Final	LD-only	40	97.0	106.8	10	.052
	LD/N	41	101.5	113.6	12	<.001
	LD/N/CEE.625	41	98.1	112.8	15	<.001
	LD/N/CEE1.25	39	102.4	117.2	14	<.001

*Within group change from baseline

As the majority of study patients would be expected to be in the lowest risk category for CHD (without CHD and with <2 risk factors), the LDL-C goal by NCEP criteria for these patients would be <160 mg/dL. Also by NCEP criteria, LDL-C levels that would require intervention other than lifestyle modification, such as drug treatment, would be levels >190 mg/dL. There were 17 patients (8%) who had an increased LDL-C ≥160 during the study. There were slightly more patients in the LD/N/CEE1.25 group who had an LDL-C ≥160 mg/dL; however as the number of patients were small overall, no conclusions will be generated from this. LDL-C increases to ≥160 mg/dL overall and by treatment group are summarized in the following table:

Table 10: M92-878 Patients with LDL-C Increases to ≥160 mg/dL During Study Treatment

		Treatment			
	All	LD	LD/N	LD/N/CEE.625	LD/N/CEE1.25
Randomized patients, n (%)	201	51	55	47	48
Patients with HDL decreases, n (%)	17 (8)	3 (6)	3 (5)	3 (6)	8 (17)

There were 4 patients (2%) with elevations in LDL-C to ≥190 mg/dL that occurred at any time during the study. These increases overall and by treatment group are summarized in the following table:

Table 11: M92-878 Patients LDL-C Increases to ≥190 mg/dL During Study Treatment

		Treatment			
	All	LD	LD/N	LD/N/CEE.625	LD/N/CEE1.25
Randomized patients, n (%)	201	51	55	47	48
Patients with LDL increases, n (%)	4 (2)	1 (2)	2 (4)	1 (2)	0

LDL/HDL Ratio

The LDL/HDL ratio increased significantly from baseline in the 3 NETA exposed group at Weeks 24 and 52, and the LD-alone group showed no significant change from baseline. Increases were relatively small however, and the majority of patients remained in a below average to average risk group for CHD. The LDL/HDL results are summarized in the following table:

Table 12: M92-878 LDL/HDL Results

Week	Treatment Group	n	Baseline	After Treatment	P-value*
24	LD-only	39	1.95	2.14	.322
	LD/N	41	2.06	2.82	<.001
	LD/N/CEE.625	41	1.92	2.95	<.001
	LD/N/CEE1.25	38	2.17	2.85	<.001
52	LD-only	23	2.05	2.32	.088
	LD/N	27	2.10	2.77	<.001
	LD/N/CEE.625	29	1.90	2.99	<.001
	LD/N/CEE1.25	23	2.14	3.04	<.001
Final	LD-only	40	1.96	2.18	.233
	LD/N	41	2.06	2.85	<.001
	LD/N/CEE.625	41	1.92	2.89	<.001
	LD/N/CEE1.25	39	2.17	2.82	<.001

*Within group change from baseline

TG

Increases from baseline in TG were seen in the LD/N/CEE.625, and LD/N/CEE1.25 groups at Week 24, and in the LD/N/CEE1.25 groups at Week 52. There was a statistically significant but clinically mild increase from baseline in TG in the LD/N group of 4% at Week 52, and a non-significant decrease from baseline in TG in the LD/N group at Week 24. The LD-alone group had no significant change from baseline in TG. The TG results are summarized in the following table:

Table 13: M92-878 Triglyceride Results

Week	Treatment Group	n	Baseline	After Treatment	Mean % change from baseline	P-value*
24	LD-only	39	107.8	117.9	9	.155
	LD/N	41	130.2	102.3	-21	.61
	LD/N/CEE.625	42	96.6	126.0	30	.012
	LD/N/CEE1.25	38	90.2	120.4	33	.089
52	LD-only	23	117.1	123.6	6	.127
	LD/N	28	123.3	128.8	4	.031
	LD/N/CEE.625	29	91.4	112.5	23	.517
	LD/N/CEE1.25	23	91.2	132.8	46	.022
Final	LD-only	40	108.5	123.5	14	.052
	LD/N	41	130.2	117.4	-10	.213
	LD/N/CEE.625	42	96.6	122.0	26	.07
	LD/N/CEE1.25	39	91.6	135.2	48	.001

*Within group change from baseline

In the short-term, TG elevations >500-600 mg/dL could be considered as clinically significant, mainly as a risk factor for pancreatitis rather than CHD. Three patients had

clinically significant elevations in TG (>500 mg/dL) during study drug treatment. Only 1 patient had a TG >600 mg/dL, patient 1158 (treatment group LD/N), who had a TG of 666 mg/dL at Day –7 prior to study drug treatment, which will not be considered as study related. Patients with TG elevations >500 mg/dL are summarized in the following table:

Table 14: M92-878 Clinically Significant Changes in TG

Patient Number	Treatment	Study Day	Days Post Treatment	Lab Value
1072	LD/N	1	-	493
1072		168	-	297
1072		365	0	583
1158	LD/N	-7	-	666
1158		187	-	491
1321	LD/N/CEE.625	-4	-	387
1321		176	-	517
1321		548	173	504

In the long-term by NCEP criteria, TG levels <200 mg/dL are desirable. Thirty-four (34) patients (17%) had TG elevations that were ≥200 mg/dL at any time during the study, and these were about equally distributed in the treatment groups, as follows:

Table 15: M92-878 Patients with TG Increases to ≥200 mg/dL During Study Treatment

		Treatment			
	All	LD	LD/N	LD/N/CEE.625	LD/N/CEE1.25
Randomized patients, n (%)	201	51	55	47	48
Patients with TG Increases, n (%)	34 (17)	9 (18)	11 (22)	7 (15)	7 (15)

d) Other Significant Results

Body weight changes can affect lipid levels, and have been shown to increase TC, LDL-C and decrease HDL-C. Mean body weight at the final treatment visit compared to baseline increased in all treatment groups. Comparisons of mean baseline weight to mean final treatment visit weight by treatment group are as follows:

Table 16: M92-878 Body Weights (lbs)

Treatment Group	n	Baseline	After Treatment	P-value*
LD-only	45	144.2	150.7	.056
LD/N	42	147.6	153.7	<.001
LD/N/CEE.625	41	145.4	155.8	<.001
LD/N/CEE1.25	42	152.2	152.8	.003

2. Study M97-777

a) Study Design

Study M97-777 was an open-label, single-arm, multi-center study in 136 female patients with endometriosis accompanied by pain. All patients received LD 3.75 mg at four-week intervals, and NETA 5 mg per day for 52 weeks. Patients received post-treatment follow-up for one year. All patients also received calcium supplements twice daily throughout the treatment and follow-up periods.

The primary and secondary efficacy endpoints were change from baseline for endometriosis-related pain parameters at each visit, change from baseline in estradiol levels, and suppression of menses. Safety endpoints included percent change from baseline in BMD at the final treatment visit (primary safety endpoint), percent change from baseline in BMD at Week 24 and Week 52, adverse events, and changes from baseline in vital signs, weight, physical examination, and laboratory tests. Serum lipid measurements for TC, LDL-C, HDL-C, and TG were obtained at baseline, at treatment Weeks 24 and 52, and during post-treatment follow-up Months 1, 2, 3, 4, 8, and 12.

Study visits and procedures are summarized in the following table:

Table 17: M97-777 Study Visits and Procedures

Procedure	Prestudy	Treatment Period						Follow-up Period		
	Days -28 to -1	Day 0	Week 4	Weeks 8, 12, 16, 20	Week 24	Weeks 28, 32, 36, 40, 44, 48	Week 52	Months 1, 2, 3, 4	Month 8	Month 12
Surgical Diagnosis of Endometriosis*	X									
Start Barrier Contraception	X									
Informed Consent	X									
Pregnancy Test	X**		X							
Physical Exam	X				X		X			
Laboratory Tests	X				X		X			
Lipid Profile	X				X		X	X	X	X
Pain Evaluation	X	X	X	X	X	X	X	X	X	X
Clinical Evaluation Symptoms/Pelvic Exam	X	X	X	X	X	X	X	X	X	X
Bone Mineral Density	X				X		X		X	X
Blood Draw for E2	X	X	X	X	X	X	X	X	X	X
Endometriosis/Menstrual/ Fertility History	X									
Medical History	X									
Review Entry Criteria	X									
Study Medication Administration		X	X	X	X	X				
Endometrial Biopsy	If clinically indicated									

*Within 12 months of entry
**Within 1 week of dosing

b) Patients Disposition

One hundred thirty-six (136) patients were entered into the study, and 82 patients (60%) completed 1 year of treatment. The disposition of patients is summarized in the following table:

Table 18: M97-777 Patient Disposition

	LD/N
Randomized, n (%)	136
Completed treatment, n (%)	82 (60)
Entered f/u Year 1, n (%)	119 (88)
Completed f/u Year 1, n (%)	64 (47)

c) Lipid results

There were mild increases in TC of +1 to +3%, and mild increases in TG (+9 to +19%). The LDL-C increased by +8 to +12%. HDL-C decreased by –16 to –18%. The results are summarized in the following table:

Table 19: M97-777 Lipid Results

		n	Baseline	After Treatment	Mean % Change from Baseline
TC					
	Week 24	117	181.2	182.6	1
	Week 52	85	180.3	185.0	3
	Final	118	181.1	184.4	2
TG					
	Week 24	117	105.4	115.1	9
	Week 52	85	104.3	123.7	19
	Final	118	104.9	120.7	15
HDL-C					
	Week 24	117	51.0	42.8	-16
	Week 52	85	51.0	41.7	-18
	Final	118	51.1	42.8	-16
LDL-C					
	Week 24	117	109.1	117.4	8
	Week 52	83	106.1	118.6	12
	Final	118	109.1	117.9	8
LDL/HDL					
	Week 24	117	2.29	2.94	-
	Week 52	83	2.25	3.10	-
	Final	118	2.29	2.98	-

The results were also analyzed by patients who completed the 52 weeks of treatment and had lipid results at the final treatment visit. These results were similar to the results overall (in Table 19) and showed increases from baseline in TC of +3%, LDL-C of +11%, TG of +17%, and an increase in the LDL/HDL ratio. HDL-C decreased from baseline by –18%. The results are summarized in the following table:

Table 20: M97-777 Mean Lipid Values at Baseline and Final Treatment Visits for LD/N Patients with Follow-up Lipid Data

Variable	n	Baseline Mean (mg/dL)	Final Treatment Mean (mg/dL)	Mean % Change from Baseline
TC	97	182.3	186.9	+3
LDL-C	97	109.8	121.6**	+11
HDL-C	97	51.4	42.1**	-18
LDL/HDL	97	2.3	3.1**	
TG	97	102.0	119.0***	+17

** = p<.001
*** = p<.01

By NCEP criteria, 64 patients (47%) had clinically significant decreases in HDL-C to <40 mg/dL that occurred during study drug treatment or during the post-treatment period. Twenty-four (24) patients (18%) had an LDL-C increase to ≥160 mg/dL, and 8 patients (6%) had increases in LDL-C to ≥190 mg/dL during study drug treatment. Four (4) of these patients (patients 803, 1805, 1908, and 1909) experienced LDL-C elevations to ≥190 mg/dL during the post-treatment period. Thirty (30) patients (22%) had elevations in TG to ≥200 mg/dL during the study, and 5 patients had TG elevations ≥500 mg/dL. Only 1 of these patients (patient 1203) experienced a TG elevation ≥500 mg/dL during study drug treatment. Two patients had elevations ≥500 mg/dL in the pre-study period prior to starting study drug (patients 909 and 2208). Patient 909 also had a TG ≥500 mg/dL in the post-treatment phase. Two additional patients (1805 and 1905) experienced TG elevations ≥500 mg/dL during the post-treatment phase.

d) Other

Mean weight at the final treatment visit significantly increased from baseline by 4.8 lbs.

Table 21: M97-777 Weight Changes Baseline to Final Treatment

n	Baseline Mean (lbs)	Treatment Mean (lbs)	p-value*
120	151.1	155.9	<.001

*Within group change from baseline

D. Discussion

The changes in the lipid profile seen with treatment with LD/N in both studies showed mean decreases in HDL-C of −16 to −19%, mean increases in LDL-C of +8 to +12%, and little effect on TC. The changes in TG were non-significant and variable. These lipid results were similar to those observed in the double-blind and open-label studies, and were consistent with results seen in previous clinical trials with 17-nortestosterone derived-progestins. As most patients likely to be treated with LD/N for endometriosis are at low-risk for CV disease, it is unlikely that the small changes seen in TC, LDL-C and TG with treatment with NETA would result in a significant change in CV risk status for these patients. This is especially true as treatment is likely to be of a relatively short duration.

The HDL-C changes, however, resulted in an HDL-C of <40 mg/dL in about 45% of patients in the NETA-exposed groups and were the most significant and consistent lipid-altering effect seen with treatment with LD/N. A decreased HDL-C has been established as a risk factor for CV disease in large epidemiologic trials; however, these studies were conducted predominantly in men and post-menopausal women, and in older patients (age >50 years). The significance of short-term, drug-induced reductions in HDL-C in pre-menopausal women at low risk for CV disease has not been determined. Studies in pre-menopausal women with OC agent use have indicated that CV events are predominantly thrombotic, not atherogenic, in nature and most strongly related to higher doses of estrogen (>50 mcg per day) and smoking. The association with the progestin type and use has not been determined. In studies of women experiencing CV events with a past history of OC use vs never-users, suggested no sustained risk for CHD after OC agents were discontinued. This suggests no lasting CV effects from estrogen/progesterone exposure. It should be kept in mind however, that no definitive studies on the long-term use of progestins or LD/N have been performed and the CV risk of 6-12 months of use (or intermittent use for 6 month periods with retreatment) is unknown.

Per NCEP guidelines, the unfavorable effects on the lipid profile must also be considered as part of overall CV risk assessment. It is reasonable to assume then, that patients with established CV risk factors at baseline, such as smoking, may be at greater risk of treatment with progestins, and should be assessed for risk factor management if treatment with LD/N is necessary and prolonged.

E. Conclusion

Questions from the consult request:

1) Has the sponsor submitted sufficient data to permit a meaningful assessment of the effects of 6 and 12 months of treatment with 5 mg of NETA per day on lipids?
   a) Is the sample size adequate?
   b) Are the laboratory measurements appropriate and adequate?

Yes, the data are sufficient, sample size was adequate, and laboratory measurements were appropriate. It can be concluded that LD/N produces decreases in HDL-C, increases in LDL-C and increases in the LDL/HDL ratio. Changes in these lipid parameters improved in the follow-up period, but did not completely return to baseline. These results were consistent between the two studies and consistent with historical data from previous clinical trials. It is also noted that the addition of CEE did not mitigate the effects on HDL-C, and that the effect on HDL-C as a function of weight gain needs to be further explored.

2) What is the assessment of the risk(s) associated with the changes in lipids that were observed after 6 and 12 months of treatment with 5 mg of NETA per day?

The absolute risk is unknown, but is likely to be small (see Discussion section).

3) Are these lipid-related risks likely to be significantly greater in women treated with Lupron plus NETA than those in women treated with Lupron alone?

It is possible that there may be some increased risk with the adverse effects of NETA on the lipid profile, but it is unlikely that women treated with LD plus NETA would be at significantly higher risk of CV disease than women treated with LD alone. The theoretical risk for CV disease needs to be balanced against the greater loss of BMD seen in women treated with LD alone.

4) If DRUDP were to extend the recommended treatment period with Lupron from 6 months to a maximum of 12 months for patients who also receive 5 mg of NETA per day, what additional warnings or precautions would be included in labeling?

It is recommended that labeling include the specific effects on the lipid profile seen with treatment with LD plus NETA. It is recommended that this include percent changes in lipid parameters, especially for HDL-C. It would also be recommended that a statement regarding low HDL-C and the increased risk of CV disease be included, although the risk in this low-risk population is not known. Women should also have a CV risk assessment (by NCEP criteria) done at baseline, and that management of other CV risk factors, such as smoking cessation, be undertaken if applicable.

F. Recommendations

It is recommended that:

1) Labeling include the effects seen on the lipid profile with treatment with LD plus NETA.
2) Labeling include a statement regarding low HDL-C and increased CV risk, although the short-term effect of treatment-induced low HDL-C levels on CV risk in endometriosis patients is unknown.
3) Labeling include a recommendation that CV risk assessment be undertaken at baseline, and that management of other CV risk factors, such as smoking, be undertaken.
4) The decrease in HDL-C as a function of weight gain should be further explored.
5) Consideration should be given to the investigation of other add-back regimens with less effect on HDL-C, such as less androgenic progestins, e.g., medroxyprogesterone.

G. Appendices

1. Study M92-878

a) Patients with LDL-C ≥160 mg/dL During the Study

Table22: M92-878 Patients With LDL-C ≥160 mg/dL During Study

Treatment	Patient Number	Treatment Day	Days Post-Treatment	LDL-C Value
LD	1233	-14	-379	
		170	-196	
		198	-168	
		366	0	
		709	343	
	1335	-8	-394	
		171	-216	
		408	21	
		668	281	
	1362	-2	-364	
		165	-198	
		358	-5	
		910	547	
LD/N	1022	-8	-94	
		87	0	
	1272	-21	-275	
		171	-84	
		307	52	
		363	108	
	1301	-7	-372	
		177	-189	
		370	4	
LD/N/CEE.625	1155	-11	-395	
		185	-200	
		385	0	
	1203	-30	-401	
		169	-203	
		375	3	
	1291	-8	-413	
		197	-209	
		406	0	
		977	571	
		1025	619	
LD/N/CEE/1.25	1044	-14	-323	
		188	-122	
		325	15	
	1085	-23	-378	
		1	-355	
		160	-196	
		356	0	
		937	581	
	1095	-20	-355	
		170	-166	
		338	2	
	1106	-29	-420	
		189	-203	

Table22: M92-878 Patients With LDL-C ≥160 mg/dL During Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	LDL-C Value
		398	6	
	1113	-23	-79	
		71	14	
	1186	-4	-374	
		167	-204	
		371	0	
	1293	-4	-212	
		188	-21	
		218	9	
	1297	-17	-405	
		183	-206	
		386	-3	
		872	483	
		1007	618	
		1119	730	

b) Patients with LDL-C ≥190 mg/dL During the Study

Table 25: M92-878 Patients with LDL ≥190 at any time during the study				
Treatment	Patient Number	Treatment Day	Days Post-treatment	Lab Value
LD	1233	-14	-379	
		170	-196	
		198	-168	
		366	0	
		709	343	
LD/N	1272	-21	-275	
		171	-84	
		307	52	
		363	108	
	1301	-7	-372	
		177	-189	
		370	4	
LD/N/CEE.625	1291	-8	-413	
		197	-209	
		406	0	
		977	571	
		1025	619	

c) Patients With HDL-C <40 mg/dL During the Study

Table 23: M-92-878 Patients with HDL<40 mg/dL During the Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	Lab Value
LD	1093	-21	-80	
		60	0	
	1111	-3	-375	
		180	-193	
		368	-5	
	1123	1	-367	
		172	-196	
		403	35	
	1157	-20	-420	
		190	-211	
		402	1	
		1060	659	

Table 23: M-92-878 Patients with HDL<40 mg/dL During the Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	Lab Value
		1137	736	
	1295	208	-224	
		432	0	
		680	248	
		952	520	
	1315	-1	-380	
		178	-202	
		380	0	
		771	391	
	1362	-2	-364	
		165	-198	
		358	-5	
		910	547	
LD/N	1003	1	-377	
		175	-203	
		378	0	
		776	398	
	1006	-5	-377	
		177	-196	
		373	0	
	1013	-17	-387	
		173	-198	
		378	7	
	1018	-47	-418	
		-4	-375	
		169	-203	
		372	0	
	1025	-12	-391	
		172	-208	
		379	-1	
	1032	-9	-129	
		142	21	
	1038	-7	-384	
		173	-205	
		376	-2	
		834	456	
		971	593	
	1042	-8	-372	
		169	-196	
		364	-1	
	1072	1	-364	
		168	-197	
		365	0	
	1084	-25	-400	
		173	-203	
		375	-1	
	1096	-10	-235	
		170	-56	
		209	-17	
	1115	-8	-93	
		86	0	
	1132	-11	-270	
		172	-88	

Table 23: M-92-878 Patients with HDL<40 mg/dL During the Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	Lab Value
	1145	1	-365	
		169	-197	
		367	1	
	1158	-7	-319	
		187	-126	
	1173	-21	-385	
		169	-196	
		365	0	
		1016	651	
	1191	-26	-392	
		171	-196	
		367	0	
	1204	-33	-398	
		170	-196	
		366	0	
	1246	-14	-412	
		183	-216	
		402	3	
		688	289	
	1251	-6	-264	
		177	-82	
	1292	-3	-403	
		190	-211	
		402	1	
	1371	186	-221	
		410	3	
		898	491	
		996	589	
		1038	631	
	1383	-28	-395	
		169	-199	
		373	5	
LD/N/CEE.625	1004	-4	-404	
		183	-218	
		410	9	
	1024	-138	-462	
		-5	-329	
		176	-149	
		337	12	
	1033	-11	-339	
		175	-154	
		328	-1	
	1073	1	-363	
		167	-197	
		363	-1	
	1077	-3	-366	
		169	-195	
		196	-168	
	1102	-13	-369	
		175	-182	
		357	0	
	1112	-14	-378	
		169	-196	

Table 23: M-92-878 Patients with HDL<40 mg/dL During the Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	Lab Value
		362	-3	
	1117	-6	-375	
		170	-200	
		373	3	
		849	479	
	1131	-14	-336	
		179	-144	
	1155	-11	-395	
		185	-200	
		385	0	
	1171	-20	-385	
		170	-196	
		366	0	
	1216	-6	-397	
		191	-201	
		219	-173	
		308	-84	
		393	1	
	1248	-7	-392	
		186	-200	
		382	-4	
		627	241	
		736	350	
	1271	-9	-378	
		170	-200	
	1291	-8	-413	
		197	-209	
		406	0	
		977	571	
		1025	619	
	1298	-11	-388	
		183	-195	
		379	1	
	1303	-20	-387	
		170	-198	
		367	-1	
	1308	-5	-385	
		171	-210	
		381	0	
	1321	-4	-378	
		176	-199	
		548	173	
	1374	-4	-180	
		178	1	
LD/N/CEE1.25	1002	-5	-372	
		171	-197	
		368	0	
	1014	-32	-378	
		-3	-349	
		155	-192	
		347	0	
	1023	-71	-427	
		-32	-388	

Table 23: M-92-878 Patients with HDL<40 mg/dL During the Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	Lab Value
		169	-188	
		358	1	
	1034	-7	-406	
		177	-223	
		400	0	
	1044	-14	-323	
		188	-122	
		325	15	
	1094	-34	-204	
		18	-153	
		173	2	
		173	2	
		214	43	
		247	76	
	1104	-22	-403	
		180	-202	
		382	0	
	1106	-29	-420	
		189	-203	
		398	6	
	1113	-23	-79	
		71	14	
	1124	-4	-370	
		170	-197	
		379	12	
	1127	-18	-375	
		163	-195	
		358	0	
	1142	-17	-393	
		172	-205	
		377	0	
	1147	-18	-238	
		162	-59	
		221	0	
	1151	-20	-413	
		184	-210	
		450	56	
	1186	-4	-374	
		167	-204	
		371	0	
	1195	-20	-245	
		170	-56	
	1201	158	-203	
		361	0	
	1232	167	-196	
		251	-112	
		363	0	
	1293	-4	-212	
		188	-21	
		218	9	
	1297	-17	-405	
		183	-206	
		386	-3	

Table 23: M-92-878 Patients with HDL<40 mg/dL During the Study				
Treatment	Patient Number	Treatment Day	Days Post-Treatment	Lab Value
		872	483	
		1007	618	
		1119	730	
	1307	-46	-190	
		16	-129	
	1313	-13	-392	
		177	-203	
		380	0	
	1322	1	-372	
		93	-280	
		178	-195	
		374	1	
		1033	660	
	1331	-3	-430	
		165	-263	
		431	3	
	1361	-66	-121	
		7	-49	

d) Patients with TG ≥200 mg/dL During the Study

Table 24: M92-878 Patients with TG ≥200 During the Study				
Treatment	Patient Number	Treatment Day	Days Post-treatment	Lab Value
LD	1093	-21	-80	
		60	0	
	1107	-22	-239	
		190	-28	
		240	22	
	1123	1	-367	
		172	-196	
		403	35	
	1157	-20	-420	
		190	-211	
		402	1	
		1060	659	
		1137	736	
	1295	208	-224	
		432	0	
		680	248	
		952	520	
	1315	-1	-380	
		178	-202	
		380	0	
		771	391	
	1362	-2	-364	
		165	-198	
		358	-5	
		910	547	
LD/N	1032	-9	-129	
		142	21	
	1038	-7	-384	
		173	-205	

Table 24: M92-878 Patients with TG >200 During the Study				
Treatment	Patient Number	Treatment Day	Days Post-treatment	Lal Value
		376	-2	
		834	456	
		971	593	
	1072	1	-364	
		168	-197	
		365	0	
	1084	-25	-400	
		173	-203	
		375	-1	
	1158	-7	-319	
		187	-126	
	1204	-33	-398	
		170	-196	
		366	0	
	1246	-14	-412	
		183	-216	
		402	3	
		688	289	
	1301	-7	-372	
		177	-189	
		370	4	
	1371	186	-221	
		410	3	
		898	491	
		996	589	
		1038	631	
LD/N/CEE.625	1004	-4	-404	
		183	-218	
		410	9	
	1041	-26	-110	
		67	-18	
	1105	213	-221	
		442	8	
	1291	-8	-413	
		197	-209	
		406	0	
		977	571	
		1025	619	
	1303	-20	-387	
		170	-198	
		367	-1	
	1308	-5	-385	
		171	-210	
		381	0	
	1321	-4	-378	
		176	-199	
		548	173	
LD/N/CEE1.25	1094	-34	-204	
		18	-153	
		173	2	
		173	2	
		214	43	
		247	76	

Table 24: M92-878 Patients with TG ≥200 During the Study				
Treatment	Patient Number	Treatment Day	Days Post-treatment	Lab Value
	1106	-29	-420	
		189	-203	
		398	6	
	1127	-18	-375	
		163	-195	
		358	0	
	1142	-17	-393	
		172	-205	
		377	0	
	1194	-23	-389	
		381	14	

2. Study M97-777

a) Patients with LDL-C ≥190 mg/dL During the Study

Table 25: M97-777 Patients with LDL≥190 During the Study			
Patient number	Treatment Day	Days Post treatment	Lab value
803	-19	-132	
	114	0	
	149	35	
	170	56	
	202	88	
	231	117	
	360	246	
	506	392	
805	-10	-122	
	118	5	
	146	33	
	174	61	
	202	89	
	230	117	
	378	265	
1303	-21	-388	
	169	-199	
	366	-2	
	403	35	
	431	63	
	459	91	
	487	119	
	611	243	
1805	-39	-403	
	177	-188	
	364	-1	
	421	56	
	458	93	
	494	129	
1908	-28	-393	
	170	-196	
	366	0	
	393	27	
	423	57	

Table 25: M97-777 Patients with LDL>190 During the Study			
Patient number	Treatment Day	Days Post treatment	Lab value
	450	84	
	478	112	
	626	260	
1909	-18	-384	
	171	-196	
	368	1	
	400	33	
	423	56	
	451	84	
	479	112	
	606	239	
2209	-7	-371	
	171	-194	
	395	30	
	423	58	
	452	87	
	480	115	
2805	-24	-387	
	168	-196	
	365	1	
	392	28	
	420	56	
	453	89	
	483	119	
	606	242	

b) Patients with TG >500 mg/dL During the Study

Table 26: M97-777 TG>500 mg/dL During the Study			
Patient number	Treatment Day	Days Post-treatment	Lab Value
909	-22	-387	
	-15	-380	
	-7	-372	
	164	-202	
	303	-63	
	367	1	
	450	84	
	485	119	
	609	243	
1203	-14	-397	
	169	-215	
	197	-187	
	252	-132	
	383	-1	
	420	36	
1805	-39	-403	
	177	-188	
	364	-1	
	396	31	
	421	56	
	458	93	
	494	129	
1907	-15	-376	
	167	-195	

	363	1
	391	29
	419	57
	447	85
	475	113
	587	225
	616	254
2208	-47	-330
	-2	-285
	175	-109

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/s/

Anne Pariser
8/17/01 10:04:30 AM
MEDICAL OFFICER

Mary Parks
8/17/01 11:55:44 AM
MEDICAL OFFICER
acting for Dr. Orloff

APPEARS THIS WAY
ON ORIGINAL

August 13, 2001

MEMORANDUM

To: Jeanine Best, MSN, RN, Project Manager; Scott Monroe, MD, Medical Officer, DRUDP, HFD-580
From: Bruce S. Schneider, MD, DMEDP, HFD-510
Through: David Orloff, MD

Subject: NDA 20-011/S-021 and 20-708/S-11 (TAP Pharmaceutical Products, Inc). Consultation regarding efficacy of norethindrone acetate (NETA, Aygestin® 5 mg tablets daily) in prevention of loss of bone mineral in women treated with Lupron® (Depot 3.75 mg IM monthly or Depot 11.25 mg IM every 3 months) for endometriosis for one year.

Background: Lupron® (leuprolide acetate) is a GnRH agonist that is approved for the treatment of pain associated with endometriosis. The hypoestrogenic state that is induced by Lupron® results in atrophic changes in the ectopic endometrial tissue, with a consequent reduction in painful symptoms. Associated with the reduction in circulating estrogens is loss of bone mineral; because of this, Lupron® treatment has been restricted to six months. Many patients are relieved of painful symptoms within a few months of treatment. Following withdrawal of the medication, some patients relapse, while others experience prolonged remissions.

One strategy for countering the loss of bone mineral that accompanies GnRH therapy is to add progestins or progestins plus estrogen to the regimen ("add-back" therapy). To permit treatment of endometriosis for up to one year, the sponsor conducted two clinical trials designed to evaluate the efficacy of "add-back" therapy in prevention of loss of bone mineral in Lupron®-treated patients. Descriptions of the two studies are presented in the consult request and in the sponsor's submission.

Study M92-878, was a randomized, double-blind, 4-arm (Lupron alone, Lupron plus NETA 5 mg/day, Lupron + NETA + CEE 0.625 mg, and Lupron + NETA + CEE 0.125 mg) trial that lasted for one year, followed by an additional 24-month period in which observational data were collected. There were approximately 50 pre-menopausal women in each study arm. Study M97-777 was an open-label, single-arm study with a 52-week treatment period followed by a 12-month observational period. All (N=136) patients received Lupron plus NETA 5 mg. The same inclusion/exclusion criteria were used for both studies. Patients were supplemented with 500 mg elemental calcium/day, without vitamin D. Thus a total of 191 patients had planned exposure to Lupron + NETA for one year. It was agreed that criteria for acceptance of efficacy were that the lower boundary of the

95 % confidence interval of the % change from baseline be > -2.2 (i.e., that the lower boundary of the 95% CI fall above –2.2).

The sponsor has conducted no dose-finding studies for NETA; dose selection was based on a prior publication that studied the efficacy of 5 mg daily. Complete descriptions of endpoints, methods of data collection and management, patient characteristics, and other parameters are included in the submission. This consultation will focus on assessment of BMD. The sponsor measured BMD at the lumbar spine (L1-L4) using DEXA. Duplicate measurements were taken with Hologic Quantitative Digital Radiography (QDR) and processed centrally by the sponsor. BMD evaluations were performed at baseline, Week 24, and Week 52. During follow-up periods BMD evaluations were planned for every four months through Month 24. There were no bone marker studies, nor were there BMD measurements made at other skeletal sites.

Results: In the following table, I have summarized patient disposition for the LD-only (Lupron alone) and LD/NETA group for M92-878 and LD/NETA for M97-777.

	STUDY M92-878		STUDY M97-777
	LD ONLY	LD/NETA	LD/NETA
Randomized	51	55	136
Completed treatment period	32 (63%)	31 (56%)	82 (60%)

The sponsor presents listings and summaries of discontinuations, including reasons for discontinuation. Apparently, the dropout rates did not differ significantly between the two treatment groups in the first study.

BMD Results of Study M92-878: BMD analyses were performed on two sets of Week 52 data. One set included only Week 52 scans of patients on therapy. The other included all week 52 scans, regardless of whether a patient was on therapy. Other analyses were performed, based on defined intervals. In addition, the sponsor carried out "Week 52 imputation analyses," in which Week 52 data were imputed for patients lacking on-treatment measurements at that time point. These used two slightly different models.

The results of these analyses are presented in the sponsor's Table 3.10a. Data are presented only for the LD-Only and LD/NETA treatment groups. The CEE groups are not presented. In the LD-Only group, there were statistically significant ($p<0.001$) declines from baseline in spinal BMD of 3.2-3.3% at 24 weeks, depending on method of calculation. At 52 weeks, the mean lumbar spine BMD had declined by about 6.3% from baseline (significant change from baseline, $p<0.001$), again depending on method of calculation and data set used. In contrast, the LD/NETA group showed mean declines from baseline of 0.2-0.3% at 6 months (within-group change from baseline NS; difference from LD-Only group $p<0.001$). At 52 weeks, the mean decline from baseline was about

0.9%. Most within-group comparisons of BMD changes from baseline at 52 weeks in the LD/NETA group were not statistically significant. The imputed analyses showed declines of 1.1%, which were statistically significant. All comparisons (using all analytical approaches) between the two treatment groups were statistically significant ($p<0.001$) at both time points. The percent changes for BMD values were quite stable across all analytical approaches.

Thus the data demonstrate that, in the LD-Only group, there was a mean loss of spinal BMD of about 3.3% at six months and 6.3% at 12 months. Patients treated with LD + NETA experienced losses of about 0.3% at six months and 0.9% at 12 months. Differences from baseline were not statistically significant in this treatment group. Between-treatment group differences were statistically significant at both time points. The data show that patients treated with LD-Only experience substantial declines in lumbar spinal BMD. These losses in spinal BMD are potentially clinically meaningful if there is no recovery when Lupron treatment is interrupted (these pre-menopausal patients are for the most part estrogen-sufficient in the absence of Lupron). The magnitude of the losses is not unexpected, given the responses of trabecular bone to estrogen withdrawal. The data also demonstrate that the BMD losses can be prevented by addition of NETA 5 mg/day.

Results of Study M97-777: The sponsor presents the results of the second study (M97-777) in several statistical tables.

One hundred thirty-six patients entered the study, and 82 (60%) completed the year of treatment. Patients without a Week 52 DEXA scan had results of their latest Treatment Period scan carried forward and included in the analysis. Other analyses included the percent changes from baseline at the Week 24 and Week 52 visits.

Irrespective of whether imputed values were used, the results were essentially the same across analyses. There were small reductions of about 0.2% from baseline at 24 weeks; these were not statistically significant. At 52 weeks, there were statistically significant ($p<0.001$) reductions from baseline of about 1.0-1.2%, depending on analytical approach to the data. In each case (Table 3.10b of the submission), the lower boundary of the 95% CI was well above –2.2. For example, for the Week 52 data collected at 7-month interval, the mean % BMD change was –1.1 (-1.6, -0.5). The data set with the greatest change, Week 52 (imputation), had a mean of –1.2% (-1.7, -0.8).

In answer to specific questions:

1. *Are the reductions in loss of BMD that are associated with NETA appropriate surrogates for maintenance of bone strength?*

NETA is a progestational agent. There are no preclinical studies that indicate that NETA increases or maintains bone strength in ovariectomized animals. Therefore, BMD changes in association with NETA therapy could not be used as a surrogate for bone quality. According to our current guidelines, NETA could not be approved for the prevention of post-menopausal osteoporosis in the absence of such studies. I recognize that this compound is likely working via an estrogenic and/or androgenic pathway in bone, and that there is little reason to believe that these effects are not associated with maintenance of bone quality. Certainly there is even less reason to suspect that bone quality is harmed by this sex steroid. Nonetheless, our guidelines would mandate the performance of these studies for prevention indication for postmenopausal osteoporosis.

In addition, the sponsor has not performed adequate (or any) dose-ranging studies. These are always required for drug approval.

In the present, rather unusual circumstance, one might consider that NETA is being used to counteract the adverse effects of an approved drug. This consideration might play a role in a regulatory decision.

Finally, NETA will be used for relatively short periods, as opposed to prevention therapies for postmenopausal osteoporosis.

2. *Is the measure of BMD at only one site (lumbar spine) in the context of the submitted studies sufficient to assess the effects of 6 and 12 months of treatment with Lupron/NETA on bone integrity?*

Loss of trabecular bone predominates in estrogen-deficient states. Thus BMD loss is most prominent at the lumbar spine. However, following estrogen withdrawal, loss of bone also occurs at the hip, wrist, and other skeletal sites. In osteoporosis prevention studies, BMD changes are always measured at important extra-vertebral sites. Thus the available information does not provide a complete picture of the overall BMD responses to Lupron and Lupron/NETA.

3. *Is the methodology (including sample size, laboratory measurements) adequate?*

I believe that the sample size was sufficient for these studies in patients with endometriosis. The duration of the trials was certainly adequate. I leave it to the medical officer in HFD-580 to decide whether the trial population was sufficiently representative. In my opinion, it was probably adequately representative. The methodology for BMD determination was standard and certainly acceptable.

4. *What is your assessment of the comparative adverse effect on bone of 12 months of treatment with Lupron + NETA, compared to 6 months of treatment with Lupron alone?*

The changes are about 1% loss at one year with LD/NETA, vs about 3% at 6 months with Lupron alone. Based on these changes alone, there is certainly no increase in bone adverse effect at one year with combination therapy, over that which is seen with standard treatment.

5. *Do you recommend adding NETA to Lupron treatment for 6 months?*

In certain individuals who are at high risk of bone loss (by BMD, personal and family history, body weight, etc.), I think that addition of NETA would be helpful in reducing any further BMD decrease at the spine at 6 months. It is likely that some individuals will experience BMD losses of more than 3% during this period, and some patients may not replace these losses. This is a medical opinion, and it should be taken in the context of the regulatory and scientific issues discussed above in Question 1.

6. *Is there any reason to believe that, in patients previously treated with a GnRH analog, re-treatment with Lupron/NETA will result in greater bone loss than in patients who had not previously been treated with a GnRH analog?*

We have data on 32 patients previously treated with a GnRH analog, who were given LD/NETA as participants in wither of the above two studies. This subset was analyzed separately. This analysis disclosed that the mean BMD loss in this group at 24 and 52 weeks was –0.515% and –0.786%, respectively. These are in reasonable agreement with the behavior of the group as a whole. Of interest, the GnRH-naïve subset lost –0.148% at 6 months and –1.136% at 52 weeks. I have no information regarding the time interval between the termination of the first GnRH treatment and the initiation of Lupron therapy. Nonetheless, it appears from the data that patients who have experienced prior GnRH therapy response as well to NETA add-back therapy as do GnRH-naïve individuals.

I hope that this consult has been helpful. If I can be of further assistance, please do not hesitate to contact me.

Bruce S. Schneider, MD
DMEDP, HFD-510

Cc Dr. Colman,

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bruce Schneider
8/22/01 02:57:07 PM
MEDICAL OFFICER

signed for D.Orloff

Eric Colman
8/22/01 03:03:42 PM
MEDICAL OFFICER
Eric Colman for David Orloff

NDA 20-011/S-021
Lupron Depot® 3.75 mg (leuprolide acetate for depot suspension)
TAP Pharmaceutical Products, Inc.

Safety Update Review – See Page 22 of the Medical Officer's Review.

/S/

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ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 020011
Trade Name: LUPRON DEPOT 3.75 mg
Generic Name: LEUPROLIDE ACETATE
Supplement Number: 021 **Supplement Type**: SE1
Dosage Form:
Regulatory Action: AP **Action Date**: 9/21/01
COMIS Indication: TREATMENT OF ENDOMETRIOSIS

Indication #1: Lupron Depot 3.75 is indicated for management of endometriosis, including pain relief and reduction of endometric lesions. Lupron depot monthly with norenthindrone acetate 5 mg daily is also indicated for initial management of endometriosis and for management of recurrence of symptoms. Duration of initial treatment or retreatment should be limited to 6 months.
Label Adequacy: Does not apply
Formulation Needed: No new formulation is needed
Comments (if any)

Lower Range	Upper Range	Status	Date
Adult	Adult	Waived	9/21/01

Comments: Endometriosis is not a condition found in the pediatric population.

This page was last edited on 9/21/01

/S/ 9/21/01

Signature Date

APPEARS THIS WAY
ON ORIGINAL

NDA 20-011, S-021
NDA 20-708, S-011
Lupron Depot 3.75 mg or 3-Month 11.25 mg with norethindrone acetate 5 mg for 12 months in the management of endometriosis.

Request for waiver for pediatric drug development.

Pursuant to 21 CFR § 314.55(c)(2)(iii), TAP Pharmaceutical Products Inc. requests for full waiver of the requirements of § 314.55(a) for pediatric use information.

These supplemental applications are for use of Lupron Depot 3.75 mg or Lupron Depot – 3 Month 11.25 mg with norethindrone acetate 5 mg daily for the management of endometriosis for 12 months.

Endometriosis is not a condition that is found in the pediatric population. As such Lupron Depot and norethindrone acetate regimen is expected to be ineffective for this indication in any pediatric age group, and qualifies for a full waiver under 21 CFR § 314.55(c)(2)(iii).

The safety and efficacy of Lupron Depot 7.5 mg, 11.25 mg and 15 mg has been evaluated in the pediatric population for the management of central precocious puberty and these strengths of Lupron Depot are approved for this indication under NDA 20-263.